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09/529,130	06/22/00	DUGGAN M	1581.0500000

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EXAMINER	
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ART UNIT	PAPER NUMBER
1553	9

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/529,130	Applicant(s) DUGGAN ET AL.	
	Examiner Chih-Min Kam	Art Unit 1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 April 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-54 and 57* is/are pending in the application.

4a) Of the above claim(s) *57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Claims

The amendment of claims 1-57 filed on June 22, 2000, Paper No. 5 is acknowledged. Claims 55 and 56 have been cancelled, and claims 1-54 and 57 are pending.

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-45 and lectins derived from plants in Paper No. 8 is acknowledged. Since the application has entered national stage processing on April 7, 2000 and restrictions is required under 35 U.S.C. 121 and 372, Examiner has rejoined Groups I (claims 1-45), II (claims 46-50) and III (claims 51-54). Examiner also recognizes galactose-binding lectins from plant, mammal and bacteria are structurally similar and patentably indistinct, thus withdraws the species election of Group I. Claims 1-54 will be examined.

The requirement is still deemed proper and is therefore made FINAL.

Informalities

The disclosure is objected to because of the following informalities:

1. At page 22, no Example 6 is described. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-27 and 32-54 are rejected under 35 U.S.C. 112, first paragraph.

Claims 1-27 and 32-54 are rejected because the specification, while being enabling for an agent (lectin-LH_N/A) comprising a galactose-binding lectin covalently linked to a fragment of

botulinum neurotoxin A (LH_N/A) comprising the L chain (L) and the N-terminal half of H chain (H_N, a membrane translocation domain), does not reasonably provide enablement for an agent comprising a galactose-binding lectin linked to a derivative of clostridial neurotoxin comprising the L chain (L) or a fragment of L chain including the active proteolytic enzyme domain and a derivative of a membrane translocation domain of H chain of a clostridial toxin or of a non-clostridial source, a method for obtaining the agent and a method of controlling the transmission of sensory information or the sensation of pain by applying the agent. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-27, 32-54 are drawn to an agent comprising a galactose-binding lectin linked to a derivative of clostridial neurotoxin comprising the L chain (L) or a fragment of L chain including the active proteolytic enzyme domain and a derivative of a membrane translocation domain of H chain of a clostridial toxin (claims 1, 2, 4-27 and 32-45) or of a non-clostridial source (claim 3), a method for obtaining the agent (claims 46-50) and a method of controlling the transmission of sensory information or the sensation of pain by applying the agent (claims 51-54). The specification, however, only discloses cursory conclusions (page 4, line 17-page 5, line 10; page 9, line 28-page 10, line 33), which state an agent of a galactose-binding lectin and a clostridial neurotoxin can be obtained by covalently attachment of lectin to a derivative of a clostridial neurotoxin with a linkage of spacer groups or can be expressed recombinantly as a fusion protein containing the required components of the agent, and the agent can reduce and prevent the transmission of pain signals from nociceptive afferents to projection neurons. The specification does not demonstrate an agent comprising a galactose-binding lectin linked to a

derivative of clostridial neurotoxin containing a fragment of L chain and a fragment of a membrane translocation domain of H chain from a clostridial toxin or from a non-clostridial source being made by either chemical or recombinant technique, nor such agent being used for controlling the sensation of pain. There is no data indicating lectin being recombinantly produced, enzymatically or chemically modified, or a fragment of L chain of a clostridial neurotoxin, or a derivative of H chain of a clostridial neurotoxin being obtained and used. The specification shows that several lectin-LH_N/A conjugates with lectins from various plants and a LH_N/A chain of botulinum toxin A have been made, these conjugates have different *in vitro* activities on inhibition of release of neurotransmitters such as substance p and glycine from eDRG (embryonic dorsal root ganglion) and eSC (embryonic spinal cord) neurons (Examples 4, 5 and 7), and one conjugate, ExL-LH_N/A has been tested *in vivo* using two rat models, an electrophysiological model of pain (see Example 8) and a behavior model of pain (hot-plate test, Example 9). The *in vitro* study using neuronal culture of eDRG neurons exhibits calcium-dependent substance P secretion and is clostridium botulinum neurotoxin sensitive and DRG neurons showed a different IC_{50} for each of the toxins tested with a 1000 fold difference between the most and least potent neurotoxins (botulinum toxin A and B, respectively, Welch et al., Toxicon 38, 245-258 (2000)). The instant application also indicates that lectin-LH_N/A conjugates with the same botulinum chain but various plant lectin have different activity and selectivity toward the response of eDRG neurons. Therefore, it is hard to predict whether a conjugate of lectin and clostridial neurotoxin would be effective even *in vitro* studies, especially with those having different botulinum toxin chains. Regarding *in vivo* studies, the specification indicates that one conjugate, ExL-LH_N/A at one dosage using intrathecal injection can reduce the

C-fibre and A_δ responses in an electrophysiological rat model of pain (Example 8 and Fig. 9) and also exhibits analgesic properties in a mouse hot-plate model (Example 9 and Fig. 10). However, these studies are performed at a single dosage using only intrathecal injection, there is no data or information regarding dose-response, time course-response and special experimental conditions described. For example, in the hot-plate test (US Patent 5,721,207) which measures hot plate latency as the analgesic response, there is no data regarding the control group, the dose-response, the time course-response, the temperature of the hot plate or other methods of administration being shown; in the electrophysiological model (Besson, Drugs 53 Suppl. 2, 1-9 (1997)) which measures C-fibre and A_δ responses as analgesic response, the response is only measured at one time point and one single dosage, there is no data regarding the dose-response and the time course-response. Therefore, it is necessary to perform further experimentaion to assess the effect of the agent for controlling the transmission of pain signal, especially the conjugates having modified structures. Despite knowledge in the art for clostridial neurotoxin and lectins, the claims encompass enormous numbers of peptides (>3500) such as modified lectins and clostridial neurotoxins which would not be expected by the skilled artisan to accomplish the method set forth. Since it is not routine in the art to engage in *de novo* experimentation where the expectation of success is unpredictable, the skilled artisan would require additional guidance in order to make and use such peptides in a manner reasonably commensurate with the scope of the claims. Without such guidance, the experimentation left to those skilled in the art is undue.

The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The

factors most relevant to this rejection are the scope of the claims, the nature of the invention, the unpredictability in the art, the the working examples, the amount of direction or guidance presented, and the amount of experimentation necessary as discussed in the preceding paragraph.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-54 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-54 are indefinite for because of the use of the terms "a derivative of a clostridial neurotoxin" and "the L-chain, or a fragment". The terms "a derivative of a clostridial neurotoxin" and "the L-chain, or a fragment" render the claim indefinite, it is unclear in the claim what kind of peptide is obtained as a derivative of clostridial neurotoxin as compared to the parent compound, and what kind of peptide is intended for the fragment of L-chain containing the active proteolytic enzyme domain. Is the derivative obtained from the neurotoxin or is it a modified form? Claims 2-54 are included in the rejection for being dependent of a rejected claim and not correcting the deficiency of the claim from which they depend.

Claim 1 is also indefinite regarding "an agent for the treatment of pain that comprises" or is it " the treatment of pain that comprises"? Two commas, one after "agent" and one after "pain" would appear to be necessary.

4. Claim 2 is indefinite for because of the use of the term "is derived from". The term "is derived from" renders the claim indefinite, it is unclear in the claim what kind of peptide is

obtained from the heavy chain of clostridial toxin for the translocation domain. The same rejection is also applied to claims 3, 7-10, 42, 48 and 49. Use of the term "is obtained from" is suggested.

5. Claims 3 and 49 are indefinite because of the use of the term "non-clostridial source". The term "non-clostridial source" renders the claim indefinite, it is unclear in the claim what the non-clostridial source is.

6. Claim 3 recites the limitation "non-clostridial source" in line 2. There is insufficient antecedent basis for this limitation in the claim 1. The same rejection is also applied to claim 49.

7. Claim 17 is indefinite as to how "recombinant technology" makes the claimed product differ from non-recombinant technology.

8. Claims 18-23, 42 and 43 are indefinite because of the use of the term "enzymatically modified", "chemically modified", "the Hc domain of H-chain is removed or modified", "modified by chemical derivatisation", "modified by mutation", "modified by proteolysis", "protein modification", "lectin protein has been modified" or "modification of the nucleic acid". The term "enzymatically modified", "chemically modified", "the Hc domain of H-chain is removed or modified", "modified by chemical derivatisation", "modified by mutation", "modified by proteolysis", "protein modification", "lectin protein has been modified" or "modification of the nucleic acid" renders the claim indefinite, it is unclear in the claim what kind of modification is performed on the peptide or nucleic acid and where the modification occurs.

9. Claims 20-24 and 32-37 are indefinite because of the use of the term "if the heavy chain (H-chain) of a clostridial neurotoxin is present" or "the H-chain, if present". The term "if the

heavy chain (H-chain) of a clostridial neurotoxin is present" or "the H-chain, if present" renders the claim indefinite, it is unclear as to what happens when the H-chain is not present, e.g., can it have a H_C domain? Or can it have H_N fragment? Claims 33-35 are included in the rejection for being dependent of a rejected claim and not correcting the deficiency of the claim from which they depend.

10. Claims 37, 40 and 47 are indefinite because of the use of the term "one or more spacer regions". The term "one or more spacer regions" renders the claim indefinite, it is unclear in the claim how many spacer regions are included.

11. Claims 39 and 40 are indefinite for because of the use of the term "clostridial neurotoxin-derived component". The term "clostridial neurotoxin-derived component" renders the claim indefinite, it is unclear in the claim which component is from clostridial neurotoxin and what kind of peptide is obtained as compared to the parent compound.

12. Claims 51-54 are indefinite because they lack essential steps as claimed in the process of controlling the transmission of sensory information. The omitted steps are: the site and method for applying the agent, the effective amount of the agent and a step whereby the desired outcome can be determined.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 1-2, 4-48 and 50-54 are rejected under 35 U.S.C. 102(b) as being anticipated by Foster *et al.* (WO 96/33273).

Foster *et al.* teach an agent containing the lectin (page 13, lines 9-13) as the TM component and a clostridial neurotoxin such as modified L chain, modified H_N and H_C of heavy chain, and the corresponding fragment (page 13, line 18-page 14, line 19) can be obtained by covalently attachment of a TM to a modified clostridial neurotoxin using linkage including one or more spacer regions (page 14, lines 1-9) or can be expressed recombinantly as a fusion protein (page 14, line 29-page 15, line 4), which meet the criteria of claims 1-2, 4-48 and 50. This agent can bind to a binding site on the surface of sensory neurons (page 12, lines 25-28) and reduce and preferably prevent the transmission of pain signals from nociceptive afferents to projection neurons (page 7, lines 15-17), therefore it can be used for controlling the transmission of sensory information or pain signals from a nociceptive afferent to a projection neuron, which meets the criteria of claims 51-54.

Conclusion

14. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (703) 308-9437. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, Ph. D. can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D. CMK
Patent Examiner

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August 12, 2001

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